SAFETY & SCIENCE OF VACCINES

IMMUNIZATION SAFETY OFFICE

The Immunization Safety Office includes six primary activities:

- Vaccine Adverse Event Reporting System (VAERS)
- Vaccine Safety Datalink Project (VSD)
- Clinical Immunization Safety Assessment (CISA) Network
- The Brighton Collaboration
- The Vaccine Technology Development (VAXDEV) Activity
- Vaccine Acceptance and Risk Perception

AS A LEADER IN IMMUNIZATION SAFETY RESEARCH and surveillance, CDC plays a vital role in assuring vaccine safety. Sound immunization policies and recommendations affecting the health of our nation depend upon continuous monitoring of vaccines and ongoing assessment of immunization benefits and risks. Serious adverse events after vaccination occur but are generally rare. Even with well designed, large, pre-licensure clinical trials, it is difficult to detect rare adverse events. Therefore, post-marketing monitoring of adverse events after vaccination is essential. Using a multi-faceted approach, CDC identifies possible vaccine side effects, conducts epidemiological studies to determine whether a particular adverse event is caused by a specific vaccine, helps determine the appropriate public health response to vaccine safety concerns, evaluates public and healthcare provider perceptions of vaccination, and communicates the benefits and risks of vaccines to the public, media, and healthcare communities.

In 2005, as part of a broad reorganization of the CDC, the Immunization Safety Branch was renamed the Immunization Safety Office (ISO) and moved from the National Immunization Program into CDC's Office of the Director, Office of the Chief Science Officer. *The reorganization was undertaken as part of CDC's efforts to create more robust immunization safety activities*. An independent operating budget was created for the Immunization Safety Office. The separation of safety monitoring and programmatic budget and reporting lines will ensure that both activities receive the attention and support needed to make certain they are equally dynamic and robust.

These steps were taken following a series of efforts by CDC to obtain input about its immunization safety activities from health professionals, scientists, policy makers, and parents:

- In 2004, CDC convened a Blue Ribbon Panel of health and safety science professionals to provide their independent assessments of CDC immunization safety activities.
- CDC heard directly from parents and concerned citizens about its autism research activities, including possible associations with vaccinations, through a series of meetings held in communities across the nation.
- CDC also asked for assessments from its own scientists and health professionals.

CDC continues to invite input from others regarding its efforts to strengthen its immunization safety focus, resource allocations, oversight and review efforts.

The functions of the six ISO primary activities and highlights of their recent accomplishments are described in the following text.

THE VACCINE ADVERSE EVENT REPORTING SYSTEM

THE VACCINE ADVERSE EVENT REPORTING SYSTEM (VAERS) is required under federal law to serve as a program for vaccine safety monitoring. It is jointly administered by CDC and the Food and Drug Administration (FDA) and functions as an "early warning" system to help identify rare vaccine side effects. VAERS accepts reports from vaccine recipients, parents and guardians, healthcare providers, and all others for any suspected adverse event following immunization, even if there is no proof that the event was caused by a vaccine. A cornerstone of vaccine safety monitoring, VAERS supports the collection, review, and analysis of reported adverse events. CDC and FDA have published and presented many vaccine safety studies based on VAERS data.

In 2005, VAERS identified Guillain-Barré Syndrome (GBS) as a possible rare serious side effect following the newly licensed meningococcal conjugate vaccine (Menactra®). Investigation of a possible causal association is currently ongoing. In the interim, the VAERS findings have resulted in educational and outreach efforts targeted to health care providers and changes to the vaccine's recommendations and instructions for use.*

Also in 2005, VAERS researchers from CDC and FDA published summaries of safety data on use of influenza vaccines in 6–23-month-old children and on the first two years of use of the live attenuated influenza vaccine (FluMist®). These safety data provide vital information in a setting in which public health authorities are considering further expanding recommendations for use of influenza vaccines and preparing for response to a possible influenza pandemic.

The VAERS program continued its work with the HHS voluntary civilian smallpox vaccination program to monitor smallpox vaccine adverse events for both civilian and military populations. VAERS monitoring helped identify myocarditis and pericarditis following vaccination and led to changes in information and educational materials for smallpox vaccines. By the end of 2005, VAERS data had supported the publication of at least five peer-reviewed journal articles which will provide the safety knowledge base for any future use of smallpox vaccine. System enhancements to VAERS in response to preparation for the smallpox program improved CDC's capacity to respond to mass immunization campaigns associated with vaccine-preventable disease threats.

General VAERS information and online reporting capability are available on the Web at *www.vaers.hhs.gov*. Secure Web-based reporting has been available since 2002 and has resulted in more timely and complete reporting to VAERS. Further evaluation of online reporting is ongoing as part of system wide quality improvement efforts. In collaboration with the Department of Defense and others, VAERS conducted the first comprehensive evaluation of healthcare provider knowledge and behaviors related to adverse events following immunization. Findings from this study will be used to develop strategies for improved education and training of potential reporters.

* *MMWR Dispatch, 10/06/05*

THE VACCINE SAFETY DATALINK

THE GAPS THAT EXIST in the scientific knowledge of and the capacity to scientifically evaluate possible vaccine adverse effects prompted the CDC to develop the Vaccine Safety Datalink (VSD) project in 1990. This project has proven to be a powerful and cost-effective tool for the ongoing evaluation of vaccine safety. The VSD project involves partnerships with several large health maintenance organizations (HMOs) to conduct high quality scientific evaluations of important immunization safety questions. VSD is an example of a large-linked database and includes information on more than six million people. All vaccines administered within the study population are recorded. Available data include vaccine type, date of vaccination, concurrent vaccinations (those given during the same visit), the manufacturer, lot number, and injection site. Medical records are then monitored for potential adverse events resulting from immunization. The VSD project allows for planned vaccine safety studies as well as timely investigations of new hypotheses. A focus of VSD research is the evaluation of the safety of new vaccines and changes in the immunization schedule. Specific VSD study questions or hypotheses result from the medical literature, the Vaccine Adverse Event Reporting System, and issues of concern to the public. Since its inception, the VSD project has resulted in scores of publications in leading medical and scientific journals, and the findings of VSD studies have had major impacts on guiding national immunization policies and recommendations.

During 2005, new methodologies that enhanced the timeliness of data availability and analysis were implemented and allowed VSD to provide rapid assessments of influenza vaccination coverage during a year of influenza vaccine shortage. The rapid assessment methodology is now being used to monitor the safety of newly licensed vaccines, such as Menactra (quadrivalent meningococcal conjugate vaccine).

SELECTED VACCINE SAFETY STUDIES IN 2005

Active Surveillance of Vaccine Safety:
A System to Detect Early Signs of Adverse Events

Davis RL, Kolczak M, Lewis E, Nordin J, Goodman M, Shay DK, Platt R, Black S, Shinefield H, Chen RT. Active surveillance of vaccine safety data for early signal detection. Epidemiology 2005; 16(3):336-41.

Recent events in the United States have underscored the need for surveillance systems that detect adverse events as soon as possible after the introduction of new vaccines or the reintroduction of old vaccines to new populations. With no population-based systems in the United States to rapidly detect adverse events to such vaccines, this study evaluated the feasibility of developing such a system. Investigators for this study used five years of data from four HMOs participating in the VSD Project. These proof-of-concept analyses indicated that the rapid detection methodology was able to detect an increase of intussusception shortly after the introduction of rotavirus vaccine. Decreases in risk for fever, seizures, and other abnormal neurologic events became detectable within 12 weeks, 42 weeks, and 18 months, respectively, after the change from DTPw (formulation with whole-cell pertussis) to DTPa (formulation with acellular pertussis).

Rapid Assessment of Influenza Vaccination Coverage Among HMO Members —Northern California Influenza Seasons, 2001-02 through 2004-05

Beginning with the 2003-04 influenza season, the VSD team and Kaiser Permanente Northern California (KPNC) established a system to apply the rapid detection methodology to monitor potential adverse events following adult and pediatric influenza vaccinations. In response to the influenza vaccine shortfall and resulting prioritization of the vaccine distribution during the 2004-05 influenza season, the rapid analysis system was utilized to allow the VSD and KPNC to carry out rapid weekly assessments of influenza vaccination coverage levels. This rapid analysis of influenza vaccination coverage indicated that KPNC effectively followed Advisory Committee on Immunization Practices (ACIP) prioritization guidelines and focused their vaccination efforts on children aged 6–23 months and persons aged 65 years and older. The final influenza vaccination coverage levels for the 2004-05 influenza season for KPNC were 57% for children aged 6–23 months, 7% for children aged 2–17 years, 6% for persons aged 18–49 years, 24% for persons aged 50–64 years, and 72% for persons aged 65 years and older.

CDC. Rapid Assessment of Influenza Vaccination Coverage Among HMO Members—Northern California Influenza Seasons, 2001-02 Through 2004-05. MMWR 2005;54(27): 676-8.

VSD Analysis on Hepatitis B Vaccine and Risk of Multiple Sclerosis

In April 2005, a VSD analysis on hepatitis B vaccine (HBV) and risk of multiple sclerosis (MS) was published as a letter in the journal *Neurology*. The analysis was done in response to a controversial study which reported finding an increased risk of MS within three years of hepatitis B vaccine administration. The study was controversial as no previous epidemiologic study had found a significantly increased risk, and the Institutes of Medicine had previously determined that the evidence favored rejection of a causal association. The VSD investigators attempted to replicate the study by reanalyzing the data from a VSD study of MS. No increased risk of MS was found in any time interval, including the first three years after hepatitis B vaccination. The study results from the VSD reanalysis support the weight of the evidence that hepatitis B vaccine does not cause MS.

DeStefano F, Weintraub ES, Chen RT. Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study (letter). Neurology 2005;64(7): 1317.

Other studies addressing important immunization safety questions that are currently in progress include:

- A multi-site case-control study of the **risk of autoimmune disease following hepatitis B vaccination**
- An assessment of the **risk of idiopathic thrombocytopenia purpura (ITP) following MMR vaccination**
- An assessment of the **safety of the inactivated influenza vaccine among children ages 6–23 months**
- Studies to determine whether **hepatitis B vaccine is associated with an increased risk of alopecia** in adults and adolescents
- A multi-site, case-control study to assess **risk of Bell's palsy following influenza vaccination**
- A multi-site, case-control study to investigate the **relationship between thimerosal and the onset of autism**
- A **follow-up neurodevelopmental assessment of children who were exposed to different amounts of thimerosal** in vaccines as infants

CLINICAL IMMUNIZATION SAFETY ASSESSMENT NETWORK

TO ADDRESS NATIONAL UNMET IMMUNIZATION safety research needs, the CDC funded the establishment of the Clinical Immunization Safety Assessment (CISA) Network in 2001. CISA is a national network of six medical research centers with expertise in immunization safety. The network includes epidemiologists, clinician researchers, and vaccine investigators who are at the forefront of their fields. The CISA network offers healthcare providers with expert opinion on immunization-related medical evaluation, diagnosis and management. The network focuses on select cases of rare vaccine adverse events that have been reported to VAERS.

The network's mission is to conduct clinical research of immunization-associated health risks to provide clinicians with evidence-based counsel and empower individuals to make informed immunization decisions. The CISA network findings will assist domestic and global vaccine safety policymakers, thereby enhancing public confidence and sustaining immunization benefits for all populations. Through these standardized case investigations, the CISA Network envisions that its research will assist in "making immunizations as safe as possible."

CISA PRIORITY ACTIVITIES FOR 2005

- Enrolling subjects in the newly established Centralized Registry of Clinical Data and Repository of Biological Specimens
- Improving our understanding of hypersensitivity reactions following immunization
- Improving our understanding of how to assess causality in relation to adverse events following immunization
- Enrolling subjects in specialized protocols such as clinical evaluation of patients with serious adverse events following yellow fever vaccine administration
- Studying unexpected or serious adverse events for newly licensed vaccines (e.g., Guillain-Barré Syndrome among adolescents who received meningococcal conjugate vaccine)
- Increasing collaboration with existing immunization safety research activities (e.g., Brighton Collaboration, Vaccine Safety Datalink, Vaccine Adverse Event Reporting System, Vaccine Acceptance and Risk Perception, as well as the Department of Defense and global collaborators).

THE BRIGHTON COLLABORATION

THE BRIGHTON COLLABORATION WAS FORMED in fall 2000 to develop case definitions for adverse events following vaccination. The Collaboration has an international membership of volunteer participants with backgrounds in patient care, academic research, public health, vaccine clinical trials, and regulatory or manufacturing issues. The Collaboration developed and published six case definitions for adverse events that are of particular concern to parents, including persistent crying, fever, hypotonic-hyporesponsive episode, intussusception, nodule at injection site, and seizure.

In 2005, the Brighton Collaboration grew from 535 to over 800 participants in 71 countries (up from 59 countries). Twelve scientific working groups are currently developing 20 case definition and guideline documents. The guidelines cover general considerations, clinical trials, data collection, analysis, and presentation for surveillance systems. In 2005, the topics the work groups addressed included anaphylaxis; fatigue; abscess and cellulitis and induration and swelling at injection site; rash; unexplained sudden death, including sudden infant death syndrome; thrombocytopenia; eczema vaccinatum; generalized vaccinia, inadvertent inoculation vaccinia, progressive vaccinia, and robust take; encephalitis/myelitis/acute disseminated encephalomyelitis and aseptic meningitis; data collection guidelines in neonatal clinical trials; and case definition with guidelines for Guillain-Barré syndrome.

More than 300 scientists have requested case definition and guidelines directly from the Brighton Collaboration for use in clinical trials and surveillance systems. Additionally, the Food and Drug Administration (FDA), the European Medicinal Agency (EMEA), and the Council for International Organizations of Medical Sciences (CIOMS) have made favorable mention for use of Brighton Collaboration case definition and guidelines in clinical trials and surveillance systems.

THE VACCINE TECHNOLOGY DEVELOPMENT ACTIVITY

THE VACCINE TECHNOLOGY DEVELOPMENT (VAXDEV) Activity focuses on a variety of technological initiatives, projects, standards, and applied research which enhance the safety of immunization, promote improved systems and practices for monitoring vaccine safety, and otherwise promote the research, development, uptake and monitoring of new and safer vaccines (*www.cdc.gov/nip/dev*).

A major priority is promoting safer, simpler, and swifter vaccine delivery technologies to overcome the following dangers and drawbacks of using needle-syringe to administer vaccine:

- Unsterile needle reuse in developing countries
- Needle phobia, discomfort to patients
- Needle-stick injuries to health care workers
- Parental resistance to increasing numbers of recommended childhood "shots"
- Sharps waste disposal complexity and costs

VAXDEV activities in 2005 included work with needle-free jet injection technologies. In order to overcome the various drawbacks and dangers of vaccination with conventional needle and syringe, VAXDEV undertakes efforts on several fronts to develop and promote vaccination by needle-free jet injection and aerosol inhalation. The Immunization Safety Office has supported the development of a new generation of safe, needle-free, high-speed disposable-cartridge jet injectors, which have reached the working prototype stage (LectraJet®) with testing completed in animals. VAXDEV collaborated with the VSD site in Seattle in their conduct of a clinical trial of influenza vaccination with standard 0.5 mL and reduced doses delivered by needle-free injectors compared to needle-syringe. The activity also implemented a vaccine study entitled "Clinical Trial of Safety (Reactogenicity) and Immunogenicity of Needle-free Jet Injection of Reduced-dose, Intradermal Influenza

Vaccine (INF) Administered to 6-Month to Under 24-Month-Old Infants and Toddlers in the Dominican Republic." This clinical trial is scheduled to begin in 2006. VAXDEV maintains a website to educate the public and serve as a scientific resource for needle-free injection technology (*www.cdc.gov/nip/dev/jetinject.htm*).

VACCINATION VIA THE RESPIRATORY TRACT

VAXDEV leads a CDC effort with multiple outside partners on research focusing on the lungs as the target tissue for antigen delivery.

Aerosol Vaccination Device: Aerosol vaccination has been shown to be an effective way to deliver measles vaccine; however, the equipment for aerosol vaccination is cumbersome and has many technical limitations. CDC developed AeroLife™ through a small business innovation research (SBIR) contract with a research engineering company. This aerosol vaccination device overcomes the previous limitations and is designed for mass measles vaccination. The device was fully successful in license-level toxicology studies. Clinical trial prototypes have been manufactured and clinical trials are expected to begin in 2006. CDC has licensed the technology to AerovectRx, Inc., a private company that intends to obtain regulatory licenses and manufacture and distribute the AeroLife™ device. Research is also underway on aerosol delivery of siRNA (small interfering Ribonucleic Acid) in collaboration with the University of Georgia. The prototype model is intended to inhibit respiratory syncytial virus.

Measles Aerosol Project: CDC is a key partner with WHO and the American Red Cross in the Measles Aerosol Project. The goal of this project is to perform the necessary toxicology research and clinical trials to license at least one aerosol device/measles vaccine combination for use in developing countries. License-level toxicology studies have been completed and clinical trials are expected to begin in India and Mexico in 2006. This project is funded by the Bill and Melinda Gates foundation for $7 million.

Measles Dry Powder Vaccine for Inhalation: Through an SBIR project, CDC worked with AktivDry, Inc. to develop a dry powder measles vaccine and test the potency in the CDC Measles Laboratory. Early dry powder measles vaccine formulations were successful in principle. CDC worked with AktivDry and many other partners including WHO, the Serum Institute of India (SII—the world's largest measles vaccine manufacturer), and the University of Colorado to develop a five-year project to refine the formulation, complete regulatory testing and establish dry powder measles vaccine production capacity. At the end of 2005, this project was funded at over $19 million under the Gates Grand Challenges in Global Public Health grant program.

VACCINE ECONOMICS

VAXDEV described a new philosophical approach and promoted a new operations research tool for vaccine purchasers to select the lowest-overall-cost formulary that will satisfy the recommended childhood immunization schedule. It competes existing and proposed monovalent and combination vaccines on distinguishing features as incentives for market-driven product innovation. VAXDEV also conducted in-house studies on vaccine wastage and collaborated with outside researchers on "willingness

to pay" surveys to assess the value of pediatric combination vaccines in reducing the number of injections.

INJECTION SAFETY

In collaboration with Emory University and Georgia Institute of Technology, NIP's Immunization Safety Office is currently researching and developing technologies to reduce the dangers of needle sticks, unsafe medical waste disposal, and unsterile reuse of needles, by studying medical waste disposal practices in Mexico. The economic benefits of these new technologies are being explored through this cooperative.

VACCINE IDENTIFICATION STANDARDS INITIATIVE

The Vaccine Identification Standards Initiative (VISI) is a cooperative effort by CDC and partners in the vaccine and immunization system, aiming to establish uniform standards for vaccine packaging, labeling, and recording. Its goal is to reduce the risk of medical errors and make it easier to accurately transfer immunization information into medical records and immunization registries. Improved recordkeeping helps researchers monitor adverse reactions following vaccination and track vaccine lots for safety surveillance. VISI guidelines include bar-coded, peel-off stickers on vaccine vials and pre-filled syringes as well as standardized requirements for information in carton sidebars. On April 26, 2004, the FDA began to require bar codes on all new unit-of-use packaging of drugs, including vaccines—an important first step toward fulfilling VISI recommendations. By April 26, 2006, such bar coding must be applied to all existing products.

VACCINE ACCEPTANCE AND RISK PERCEPTION ACTIVITIES

THE VACCINE ACCEPTANCE AND RISK PERCEPTION (VARP) team conducts ongoing research to

- Better understand how individuals interpret risks and make vaccination decisions
- Determine how best to communicate with different groups of people about the need for vaccination and the risks and benefits of vaccines
- Develop and evaluate interventions that help individuals make informed decisions about vaccinations

Research is underway to address each of these goals. In 2005, an international study in collaboration with the World Health Organization was initiated to better understand the vaccine safety perceptions of parents in developing countries. Staff visited three countries, Kazakhstan, Uzbekistan and Uganda, working with in-country public health staff to conduct a survey of parents.

Also in 2005, efforts were continued to develop and test tailored educational materials for parents about childhood immunizations. An increasing number of parents, as well as healthcare providers, have little or no personal experience with or knowledge of many of the diseases that childhood immunizations prevent. Perceptions regarding the need for vaccines may therefore become discordant with current immunization recommendations. Many parents need and want to know the rationale for the immunizations and to understand the risks. VARP's objective is to encourage

a shift from a strategy of "make it (immunization) obligatory" to a campaign of "make it real": make the need for the vaccines real, the name of the vaccine real, the disease the vaccine prevents real, the vaccine risk real, and the consequences of not vaccinating real. The goal is to have the parent become a partner in vaccine decisions and an active participant in the health of their child as well as in the public health of the community.

VARP scientists completed and published a variety of vaccine acceptance and risk perception studies in 2005, including:

- A survey of immunization attitudes and beliefs among parents
- Parent attitudes toward immunizations and healthcare providers: the role of information
- Parental vaccine beliefs and child's school type.
- Vaccine beliefs of parents who support and oppose mandatory vaccination.
- Factors influencing African-American mothers' concerns about immunization safety: a summary of focus group findings in Atlanta.

IMMUNIZATION SCIENCE

IMMUNIZATION SCIENTIFIC ACTIVITIES CONDUCTED or sponsored by NIP include conducting disease surveillance, investigating disease outbreaks, evaluating practices for immunization delivery, investigating improved technologies for immunization, and conducting social and behavioral research related to immunization. NIP also prepares immunization recommendations and communicates these findings to appropriate audiences. Immunization science addresses how we learn about immunization that helps protect everyone from vaccine-preventable diseases.

CONTINUING THE COMMITMENT TO IMMUNIZATION SCIENCE

Throughout NIP's history, practical, solution-oriented research has been on the rise. Today, more than 250 research projects are underway. Of these, most involve external partners. In collaboration with these partners, NIP is investigating:

- Impacts of newer vaccines, such as varicella and pneumococcal conjugate vaccine, in reducing and eliminating disease as coverage increases
- How well new vaccines work among special populations, such as children with asthma or sickle cell disease
- Better ways to protect infants and adults against diseases such as whooping cough
- The best way to design and conduct studies to uncover any rare adverse events that may follow immunization
- Monitoring the safety of several new vaccines
- Using computer models to predict the impact of vaccination in the event of a biological attack
- How vaccine shortages affect doctors' practices
- The reasons for racial or ethnic disparities in adult immunization coverage
- Improving the business processes for using computers to track children's vaccinations

- Finding the best ways to translate the success of vaccination to developing countries
- Promoting development of safer, needle-free immunization technologies, such as disposable-cartridge jet injectors and aerosolized vaccines, for mass vaccination campaigns and routine immunization
- Conducting clinical vaccine trials of needle-free jet injection to assess the safety, immunogenicity, user preferences, and feasibility of this method

VACCINE ECONOMIC STUDIES

In 2005, NIP continued its use of economic analyses to understand the complexity of the U.S. immunization system as well as immunization systems worldwide. Examples of studies related to the economic impact of immunization currently underway include:

Internal Studies

- Studying vaccine markets from development to commercialization
- Cost-benefit analyses of the routine childhood immunization schedule
- Cost estimation of mass vaccination clinics to identify efficient size
- Cost estimation of immunization registries to identify opportunities to improve efficiency

External Studies

- Joint Initiative in Vaccine Economics: estimation of the morbidity associated with varicella zoster; how states vaccination programs make vaccine provision decisions; economic study of global polio eradication: vaccine stockpiling and outbreak response modeling; estimation of the morbidity associated with adult influenza
- Studying the factors associated with uptake of clinical immunization standards
- Estimating the cost-effectiveness of childhood immunization strategies

NEW VACCINE SURVEILLANCE NETWORK

NIP's success in conducting practical, results-oriented research stems in part from continuing efforts to establish research partnerships and funding opportunities. With the right details in place—the personnel, facilities, and funding—research can be more timely, quickly answering pertinent questions for medical care providers and immunization policy makers. The New Vaccine Surveillance Network (NVSN), established in 1999, is one example of the many research efforts NIP sponsors. This network of sites investigates the impact of new vaccines and new vaccine policies on children who are hospitalized or are seen in emergency department outpatient settings. Along with other studies, NVSN is currently analyzing the burden of respiratory disease among young children. Researchers working in nine counties in three areas (Rochester, Cincinnati, and Nashville) discovered that children under age 5 are hospitalized for acute respiratory illness at the rate of 18 out of every 1,000 children, with respiratory syncytial virus (RSV) infections, parainfluenza, and influenza causing most of the disease. These data, supporting a high rate of hospitalization associated with influenza, were instrumental in a 2003 policy change to recommend flu vaccination routinely for all children age 6–23 months, effective Fall 2004. Vaccines for RSV and parainfluenza are in clinical trials. In the future, the NVSN will assess whether a reduction in the number and severity of acute respiratory illnesses occurs attributable to recommended vaccinations.